

AMENDMENT TO THE CLAIMS

▪ **Format of Claim Amendments**

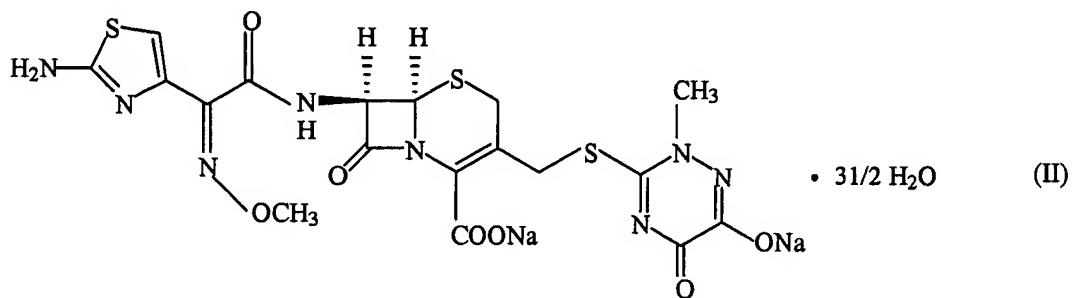
Applicants have amended the claims to introduce new claims 18-22 pursuant to the revised format to 37 C.F.R. 1.121, which was officially adopted by the USPTO in July of 2003, Applicants herein submit only one version of the claims with a detailed listing of all original and new claims in the application.

▪ **Statement with Respect to Scope of Amended and Non-Amended Claims**

Amendments to, cancellation of, and additions to, the claims are made in order to streamline prosecution of the case to embodiments that are presently anticipated to be of commercial significance, and are not made for a purpose of patentability. Any amendment, cancellation or addition made herein should not be construed in any manner as indicating Applicants' surrender of any subject matter of the application, or surrender of any equivalent to any element asserted in one or more claims. Applicants do not concede that the scope of the claims set forth below fail to extend as far as the original claims. Furthermore, any narrowing which may be evinced with respect to subject matter covered by the claims as a whole, or by one or more claims of the appended claims, when compared to claims previously in the application, should not be interpreted as indicating that the Applicants have generally disclaimed the territory between the original claimed subject matter and the amended claimed subject matter. Applicants intend each term of the claims set forth below to be read with respect to the full-breadth of the language of the claims and not to be confined to a strict literal read of amended terms. Amended claims elements are to be construed to include substantial equivalents known to those of ordinary skill in the art. Applicants assert that the amendments are made without prejudice and reserve all rights to prosecute any canceled claims, and claims preceding any amendment, and other disclosed (but not presently claimed) embodiments in the application, in future continuation applications, divisional applications, continuation-in-part applications, continuing prosecution applications, requests for continuing examination, re-examination applications and any other application claiming priority from or through the present application.

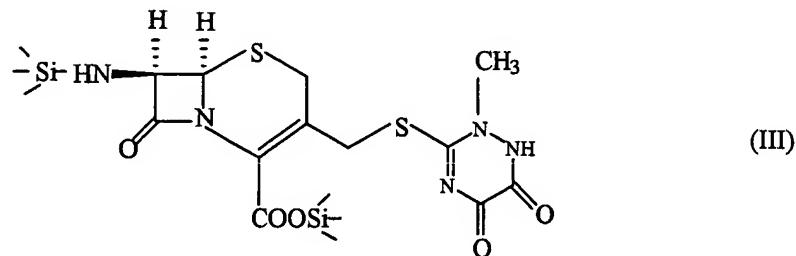
**COMPLETE LIST OF CLAIMS THAT ARE OR HAVE BEEN BEFORE THE OFFICE
AFTER ENTRANCE OF THE AMENDMENTS MADE HEREIN**

Claim 1: (Original) In a process for preparation of ceftriaxone sodium of formula (II),

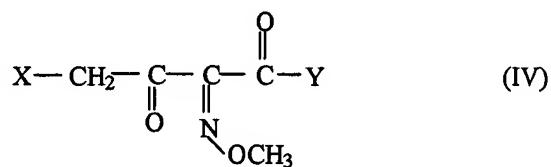


comprising the steps of

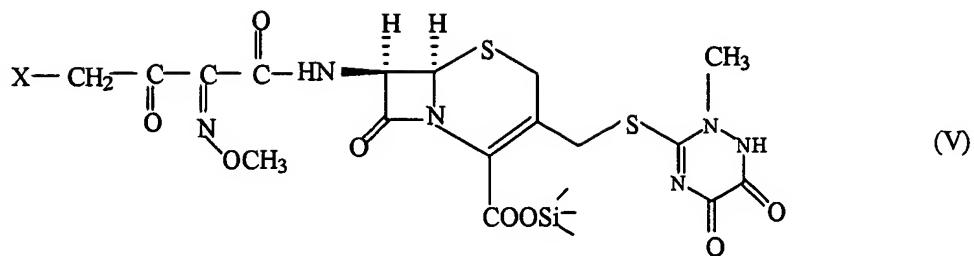
i) reacting a silylated compound of formula (III),



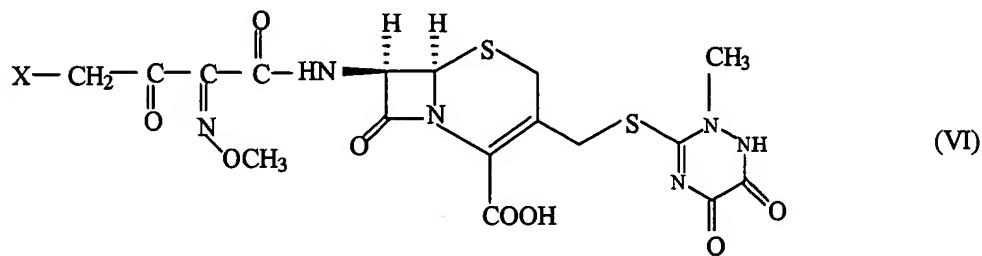
with a 4-halo-2-methoxyimino-3-oxo-butyric acid derivative of formula (IV),



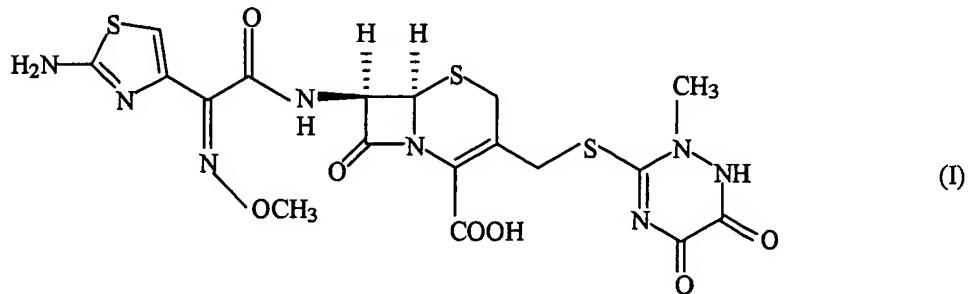
wherein X and Y represent a halogen atom to give a compound of formula (V),



ii) desilylating the compound of formula (V), wherein X is as defined hereinabove to give the desilylated compound of formula (VI),

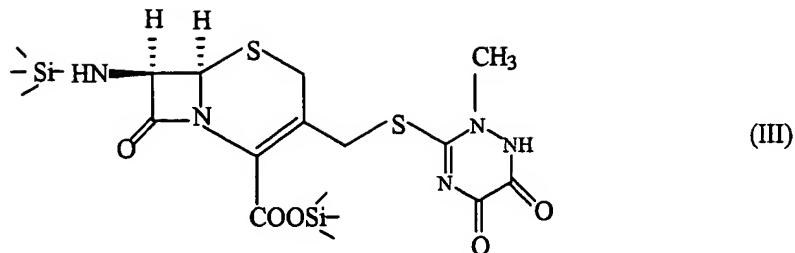


iii) reacting the desilylated compound of formula (VI) with thiourea in a solvent system containing organic solvent and water, to obtain ceftriaxone of formula (I),

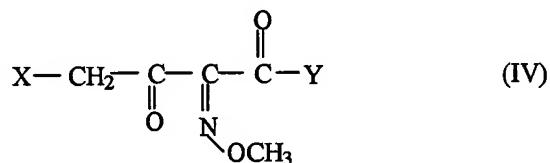


iv) converting the compound of formula (I) to the sodium salt (II); **wherefore the improvement comprises**

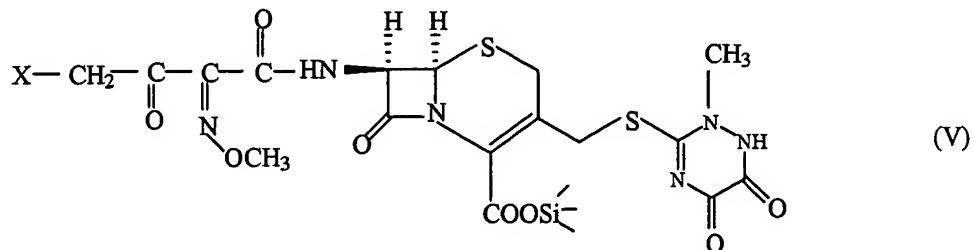
i¹) reacting a silylated compound of formula (III),



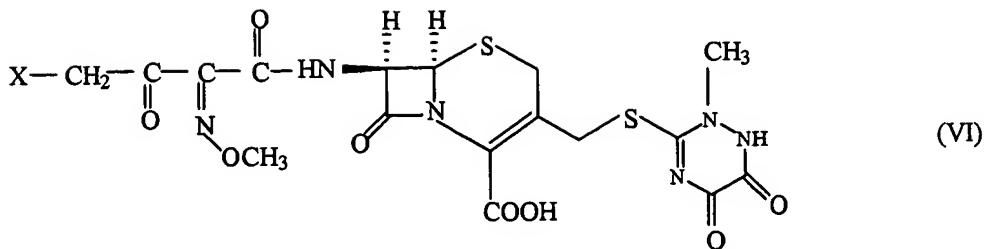
with a 4-halo-2-methoxyimino-3-oxo butyric acid derivative of formula (IV), having a purity of at least 95% and containing di- and poly-brominated compounds less than 0.50%,



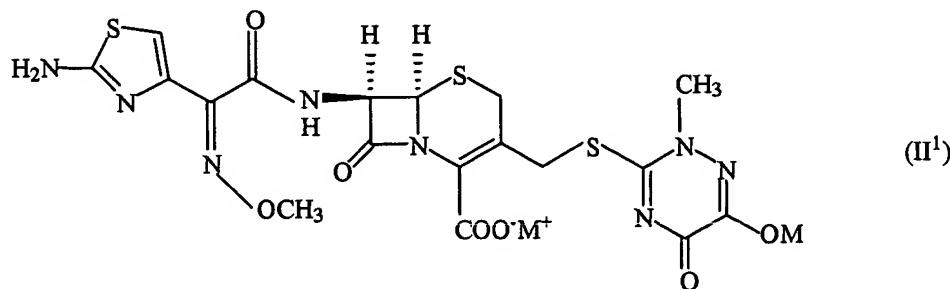
wherein X and Y represent a halogen atom in the presence of an inert water-immiscible organic solvent or mixtures thereof and in the presence of an acid scavenging agent at a temperature of between -10° C to -0° C to give a compound of formula (V),



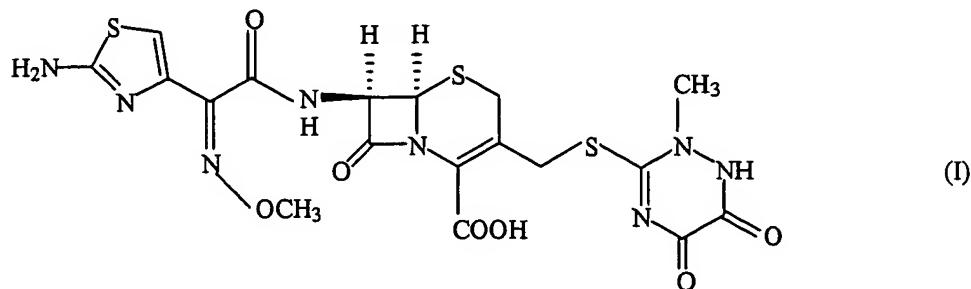
ii¹) adding the solution of compound of formula (V) in the inert water-immiscible organic solvent or mixtures thereof to a 1:1 mixture of water and a water-immiscible organic solvent and separation of the organic phase to provide a solution of compound of formula (VI) in the inert water-immiscible organic solvent or mixtures thereof,



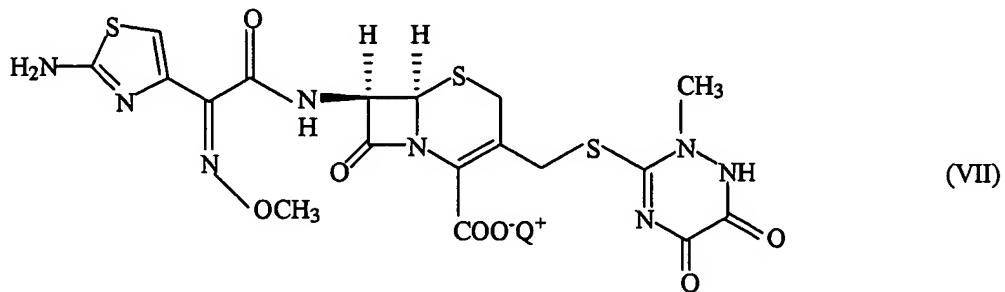
iii¹) reacting the solution of compound of formula (VI) in the inert water-immiscible organic solvent or mixtures thereof with a solution of thiourea in water in the presence of an alkali metal containing inorganic base at a temperature of between 0° C to +10° C at a pH ranging between 5.0 to 5.5 and separation of the organic layer to provide a solution of the alkali metal salt of ceftriaxone of formula (II¹) in water, wherein M is an alkali metal,



iv¹) mixing the solution of the alkali metal salt of ceftriaxone (II¹), wherein M is as defined herein earlier in water with a water-immiscible organic solvent and a water-miscible solvent and treating the solution thus obtained with an acid to a pH of 3.6 to 4.0 and isolating the precipitated ceftriaxone of formula (I) by filtration,

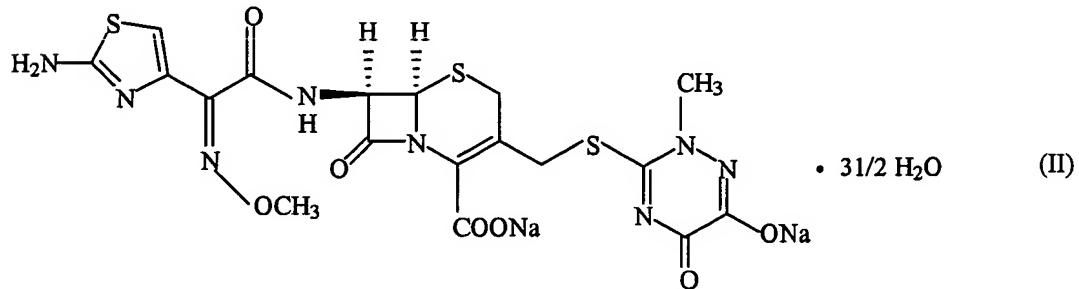


v¹) reacting a solution of ceftriaxone of formula (I) in water with an organic amine maintaining a pH of 5.4 ± 0.2 to produce a solution of the amine salt of ceftriaxone in water of formula (VII),



wherein Q represents the organic amine, and

vi¹) reaction of the amine salt of ceftriaxone of formula (VII) in a mixture of water and a water-miscible organic solvent with a sodium metal carrier to give ceftriaxone sodium of formula (II), substantially free of impurities and having low Color absorbance.



Claim 2. (Original) A process according to claim 1, in which in step i¹), the inert water-immiscible organic solvent is selected from chlorinated hydrocarbons, acetic acid (C₁₋₄) alkyl esters and ethers.

Claim 3. (Original) A process according to claim 1, in which in step i¹), wherein the acid scavenging agent is selected from ethylene oxide, propylene oxide, butylene oxide,

acetamide, epichlohydrin, calcium oxide, disodium hydrogen phosphate, calcium carbonate and quaternary ammonium phosphates.

Claim 4. (Original) A process according to any one of claims 1 and 2, wherein the preferred acid scavenging agent is acetamide.

Claim 5. (Original) A process according to any one of claims 1, 2 and 3, wherein the acid scavenging agent is employed in molar proportions of 1.0 to 3.0 moles per mole of compound of formula (III).

Claim 6. (Original) A process according to any one of claims 1, 2, 3 and 4, wherein the acid scavenging agent is employed in molar proportions of 1.0 to 1.5 moles per mole of compound of formula (III).

Claim 7. (Original) A process according to claim 1, in which in step ii¹), the water-miscible organic solvent is selected from tetrahydrofuran or acetonitrile.

Claim 8. (Original) A process according to claim 1, in which in step iii¹), thiourea is employed in molar proportions of 1.0 to 3.0 moles per mole of compound of formula (III), preferably in molar proportions of 1.0 to 1.5 moles per mole of compound of formula (III).

Claim 9. (Original) A process according to claim 1, in which in step iii¹), the alkali metal inorganic base is selected from sodium hydroxide, potassium hydroxide, lithium hydroxide, sodium carbonate, potassium carbonate, lithium carbonate, sodium hydrogen carbonate, potassium hydrogen carbonate and lithium hydrogen carbonate.

Claim 10. (Original) A process according to any one of claims 1 and 9, wherein the alkali metal containing inorganic base is employed in molar proportions of 2.0 to 5.0 moles per mole

of compound of formula (III), preferably in molar proportions of 2.0 to 3.0 moles per mole of compound of formula (III).

Claim 11. (Original) A process according to claim 1, in which in step iv¹), the water-immiscible organic solvent is selected from chlorinated hydrocarbons, acetic acid (C₁₋₄) alkyl esters and ethers.

Claim 12. (Original) A process according to claim 1, in which in step iv¹), the water-miscible organic solvent is selected from tetrahydrofuran, acetonitrile or a C₁₋₄ lower alcohol.

Claim 13. (Original) A process according to claim 1, in which in step v¹), the organic amine is selected from diethylamine, triethylamine, diisopropylamine, cyclohexylamine, pyridine, 2,4-dimethylamino pyridine and N-methyl morpholine.

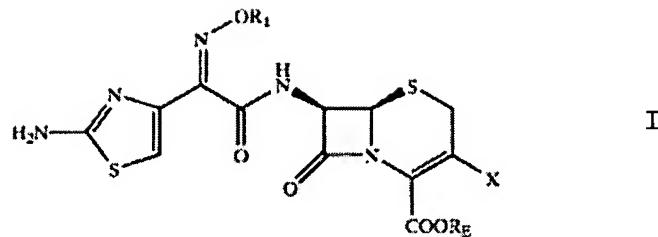
Claim 14. (Original) A process according to claim 1, in which in step vi¹), the water-miscible organic solvent is selected from tetrahydrofuran, acetonitrile, a C₁₋₄ lower alcohol and a ketonic solvent.

Claim 15. (Original) A process according to claim 1, in which in step vi¹), the sodium metal carrier is selected from sodium acetate, 2-ethyl sodium hexanoate and 2-ethyl sodium octanoate.

Claim 16. (Original) A process according to claim 1, wherein the ceftriaxone sodium of formula (II) has a Color absorbance of 0.04 to 0.05 AU at 450 nm.

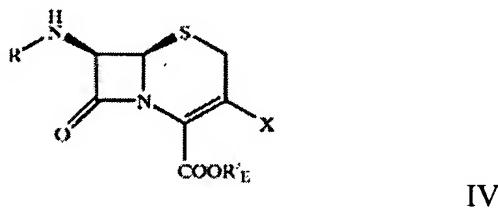
Claim 17. (Original) A process according to claim 1, wherein the level of total impurities in ceftriaxone sodium (II) obtained is the range of between 0.05 to 0.20%.

Claim 18. (New) A process for the production of a compound of formula

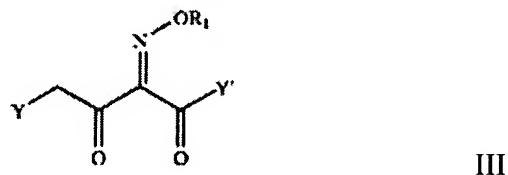


wherein X and R₁ are substituents useful in cephalosporin chemistry and R_E is hydrogen, a negative charge or together with the COO— group to which R_E is attached is an ester; comprising

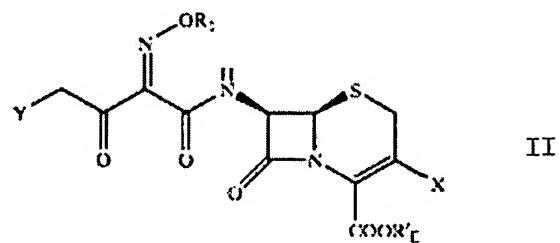
i) reacting a compound of formula



wherein R is hydrogen or silyl, R'_E is silyl or together with the COO— group to which R_E is attached is an ester; and X is as defined above, with a compound of formula



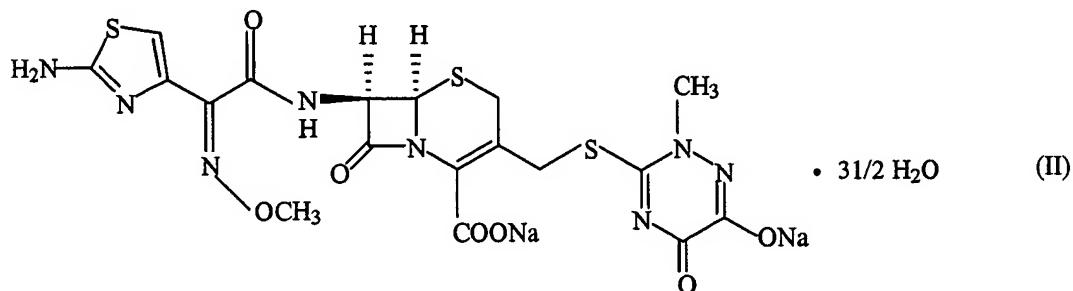
wherein Y is halogen, Y' is a group which forms a basis that a compound of formula III is in a reactive form; and R₁ is as defined above, to obtain a compound of formula



wherein Y, X, R'_E and R₁ are as defined above;

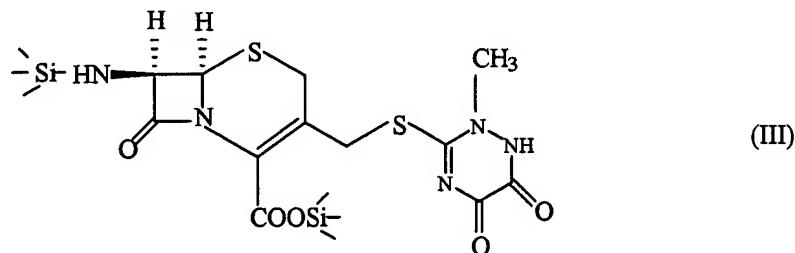
ii) desilylating a compound of formula II wherein Y, X, R'_E and R₁ are as defined above, and reacting a desilylated compound of formula II with thiourea in a solvent system containing organic solvent and water; to obtain a compound of formula I.

Claim 19. (New) A process for preparation of ceftriaxone sodium of formula II,

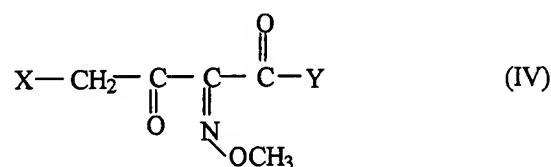


comprising the steps of:

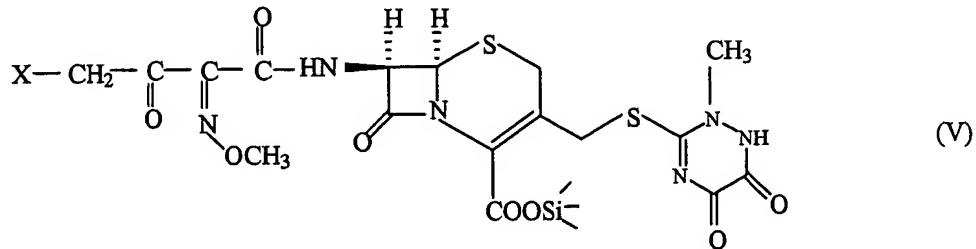
i) reacting a silylated compound of formula III,



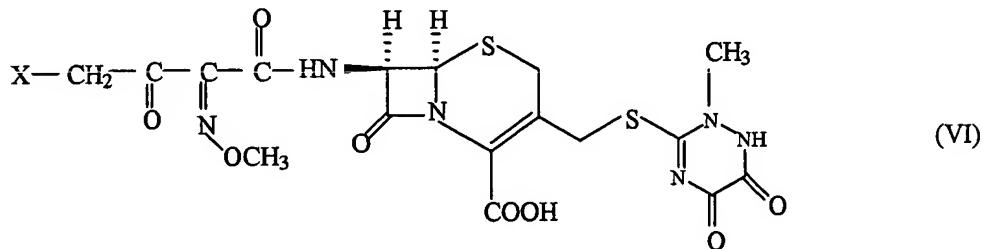
with a 4-halo-2-methoxyimino-3-oxo butyric acid derivative of formula IV, having a purity of at least 95% and containing di- and poly-brominated compounds less than 0.50%,



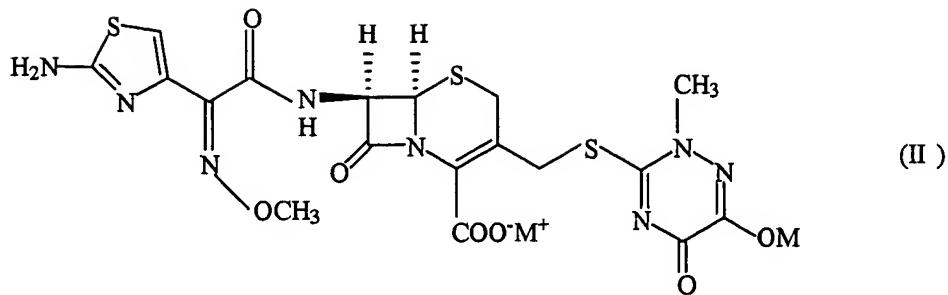
wherein X and Y represent a halogen atom in the presence of an inert water-immiscible organic solvent or mixtures thereof and in the presence of an acid scavenging agent at a temperature of between -10° C to -0° C to give a compound of formula V,



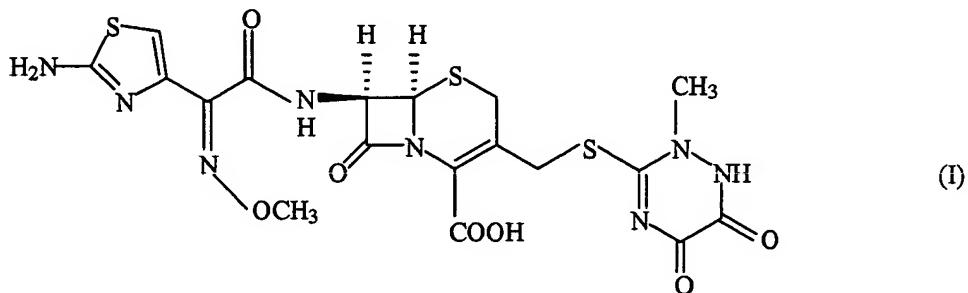
ii) adding the solution of compound of formula V in the inert water-immiscible organic solvent or mixtures thereof to a 1:1 mixture of water and a water-immiscible organic solvent and separation of the organic phase to provide a solution of compound of formula VI in the inert water-immiscible organic solvent or mixtures thereof,



iii) reacting the solution of compound of formula VI in the inert water-immiscible organic solvent or mixtures thereof with a solution of thiourea in water in the presence of an alkali metal containing inorganic base at a temperature of between 0° C to +10° C at a pH ranging between 5.0 to 5.5 and separation of the organic layer to provide a solution of the alkali metal salt of ceftriaxone of formula II in water, wherein M is an alkali metal,

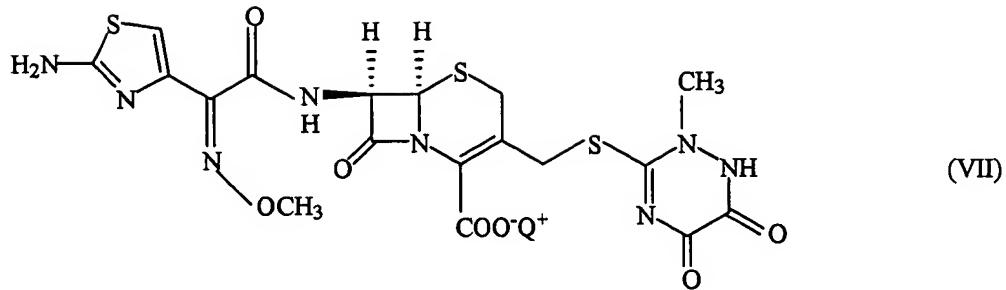


Claim 20. (New) The process according to claim 19, further comprising the step of mixing the solution of the alkali metal salt of ceftriaxone of the formula II, wherein M is as defined herein earlier in water with a water-immiscible organic solvent and a water-miscible solvent and treating the solution thus obtained with an acid to a pH of 3.6 to 4.0 and isolating the precipitated ceftriaxone of formula I



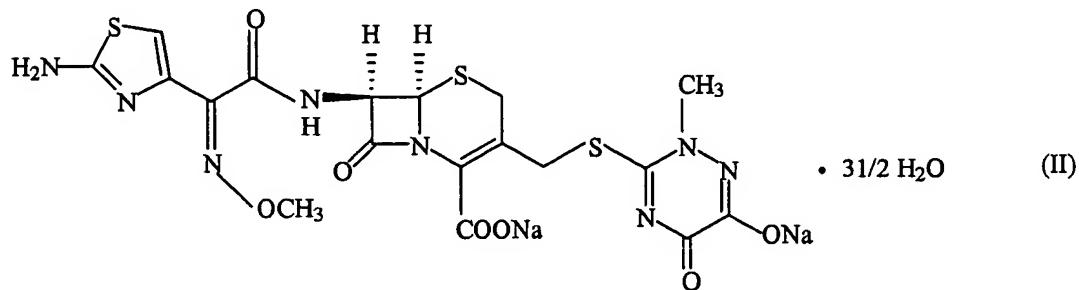
by filtration.

Claim 21. (New) The process according to claim 20, further comprising the step of reacting a solution of ceftriaxone of formula I in water with an organic amine maintaining a pH of 5.4 ± 0.2 to produce a solution of the amine salt of ceftriaxone in water of formula VII,



wherein Q represents the organic amine.

Claim 22. (New) The process according to claim 21, further comprising the step of reacting an amine salt of ceftriaxone of formula VII in a mixture of water and a water-miscible organic solvent with a sodium metal carrier to give ceftriaxone sodium of formula II



substantially free of impurities and having low color absorbance.